PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
H 3096 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/002506	09.03.2005	10.03.2004

International Patent Classification (IPC) or national classification and IPC
INV. B65B55/00 B05C3/00 A61J1/00 A61L27/28 A61L27/54 A61L31/08 A61L31/16

Applicant
SCIL TECHNOLOGY GMBH et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.12.2005	31.07.2006
Name and mailing address of the international preliminary examining authority:	Authorized officer
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/002506

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-40 as originally filed

Claims, Numbers

1-50 received on 19.12.2005 with letter of 16.12.2005

Drawings, Sheets

1/13-13/13 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/002506

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☒ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-18, 24-27, 44-48, 50 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10, 11, 15, 24-27,
	No:	Claims	1-9, 12-14, 16-18, 44-48, 50
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18, 24-27, 44-48, 50
Industrial applicability (IA)	Yes:	Claims	1-18, 24-27, 44-48, 50
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV: Non-unity

1. This International Preliminary Examining Authority considers that there are two inventions covered by the claims indicated as follows:

I: Claims 1-18, 24 to 27, 44 to 47, 48 (part) and 50 (part) directed to a method of coating a device, and the coated device obtained by said method

II: Claims 19-23, 28-43, 48(part), 50(part) directed to a packaging container.

As pointed out in the Search Report and in the Written Opinion of the International Searching Authority wherein both inventions have been dealt with, the present application contains two separate inventions which are not so linked as to form a general inventive concept (Rule 13.1 PCT) for the following reasons:
The problem underlying the present invention is to provide an improved method for coating a device with a substance, especially with a pharmaceutically active substance, wherein the substance is deposited quantitatively and homogeneously onto the device (cf. p.5, l.7 to 13 of the description).

According to the **first aspect** of the application, the above-mentioned problem has been solved by a method comprising the following steps: (1) contacting the device into a solution of said substance, and (2) drying said device while being in contacting said solution. It should be emphasized at this point that the drying step, in particular the way of carrying out this step is still unclear.
Preferably an antioxidant in the form of methionine in added to the coating solution which as demonstrated in examples 5 and 7 avoids degradation and oxidation of the protein used as active substance (cf. p. 4, l. 23 to p.5, l.5 of the description and fig. 7,8).

According to the **second aspect** of the application, a homogeneous distribution of the active substance such as peptide rhGDF5 onto the substrate can be achieved when the coating process is carried out in a specific siliconized container (cf. Ex.8, fig.9).

Since two completely different solutions (1. two step coating method, and 2. use of

siliconized container) have been suggested to solve the problem underlying the present application, these solutions, a priori, relate to two separate inventions which are not so linked as form a single inventive concept.

Having regard to W 39/90 and to W33/92, it is not the form of reference, but the actual content of the claims which established technical relationship between the subject-matter of different claims, and which is thus decisive for the question of unity. Accordingly, amended claim 28 which has been linked to main claim 1 does not overcome the non-unity objection.

The application does therefore not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

Hence the **first invention** therefore relates to a method of coating of a device with a substance comprising step (a) wherein the device is brought into contact with a solution of said substance and a step (b) wherein said device is dried as defined in claims 1 to 18, and 24 to 27, and to a coated device obtainable by the method as set out in claims 44 to 47, 48 (part), and 50 (part) while
the **second invention** relates to a container coated with an inert repelling material , such as silicone or PTFE as described in claims 28 to 43 as well as with the use of said container in a coating process (cf. claims 19 to 23).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents

D1: US 2003/204239 A1 (CARLYLE WENDA ET AL) 30 October 2003 (2003-10-30)

D2: WO 03/043673 A (SCIL BIOMEDICALS GMBH; KOHNERT, ULRICH; POEHLING, SYLKE; HELLERBRAND,) 30 May 2003 (2003-05-30)

D3: WO 02/39946 A (SMITH & NEPHEW, INC) 23 May 2002 (2002-05-23)

D4: US-A-5 335 769 (KLOKKERS-BETHKE ET AL) 9 August 1994 (1994-08-09)

D5: WO 00/21745 A1 (ARJO WIGGINS S.A.) 20 April 2000 (2000-04-20)
D6: EP-A-1 072 321 (ARZNEIMITTEL GMBH APOTHEKER VETTER & CO. RAVENSBURG) 31 January 2001 (2001-01-31)

1. Novelty of the First invention

The first invention of the present application which relates to a method of coating a device does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 9, 12 to 14, 16 to 18, 44 to 48, and 50 is not new in the sense of Article 33(2) PCT.

The document D1 discloses a stent coated with a so-called preservative coating comprising a bioactive agent which may be selected from protein, protein analog, saccharide and derivatives thereof (cf. D1, [0008]), a polymeric matrix (cf.D1, [0037]), and a preservative including at least one antioxidant (cf. D1, [0012]).The coating is applied to the stent by dipping, spraying or painting the drug and preservative-containing solution (cf. D1, [0012[, [0050], Fig.4).

D2 describes a method of coating a device comprising the steps of providing a protein solution, contacting said solution with a carrier containing calcium phosphate and drying the coated carrier(cf. D2, p.6, 3rd para to p.7, 1st para).

2. Inventive Step of the First Invention

The first invention of the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 18, 24 to 27, 44 to 48 and 50 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as being the closest prior art since it relates to stabilized drug polymer coatings which prevents degradation of the drug within the polymer due to the presence of at least one antioxidant (cf. D1 [0003], [[0004]). The antioxidants mentioned in D1 (cf. D1 [0008]) are identical with those mentioned in the present application with the exception of methionine (cf. p. 22, l.14 to 18 of the description).

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative or further antioxidant which cannot be considered as involving an inventive step due to lack of any surprising or unexpected effects over the antioxidants used in the art.

Further, the use of a certain drying operation as mentioned in claim 10, the adjustment of a vacuum, a certain pressure or a certain temperature, and the use of a specific apparatus as mentioned in claims 24 to 27 are part of routine activities of the skilled man to carry out a coating process. Such activities do therefore not impart an inventive step.

Re Item VI

WO2005/016399, although not constituting prior art within the meaning of Rule 64.1 (b) , appears to disclose all the features of claims 1 to 8, 12, 14, 16 to 18, 44, 45, 47, 48 and 50 (p.2, [0012], p.4, [0024], p.6[0032],[0033]).

Re Item VIII: Clarity

Claim 1 does not fulfil the requirements of Art. 6 PCT since it is completely unclear how and under which circumstances a device can be dried while being in contact with an solution comprising an aqueous or organic solvent.

The applicant referred to Figure 1 and to the explanations given on page 27. In said passage it is disclosed that an implant like a screw is inserted into a container (a siliconized vessel), and thus completely surrounded by the liquid. It is further explained that a stopper is placed in an intermediated position and that the drying step is started which results in the device being coated. The last part of the last sentence represents a functional definition of the drying operation failing to indicate any concrete information how the drying process is carried out.
The only information given in said passage can be found in the following sentence saying that due to the semi-closed position of the stopper, it is possible that for example water can escape from the container during drying process. In that case during and after escape of the water, the device (or at least part of it) will not be further in contact with the aqueous solution. Thus it is still unclear how during

progressive drying , the device will be still in contact with the coating solution, and consequently how the whole coating process is carried out.

In addition, it is clear from the description that the addition of an antioxidant is essential to the definition of the first invention (cf. p.22, l.14-18; Ex. 5, 7). Since independent claim 1 does not contain this feature, it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

Claims 48 and 49 are unclear with regard to the category of said claims.

Claims

1. Method of coating of a device with a substance comprising the steps of:
   (a) contacting said device into a solution of said substance, and
   (b) drying said device while being in contacting said solution.

2. The method of claim 1, further comprising the step of removing volatile components from said solution of said substance.

3. The method of claim 2, wherein said removal step is performed before, simultaneously, or after step (b).

4. The method of claim 1, 2 or 3, wherein said substance is a pharmaceutically active substance.

5. The method of claim 4, wherein said pharmaceutically active substance is a protein, peptide, polysaccharide or a glycolipid or a small molecule.

6. The method of claim 5, wherein said pharmaceutically active substance is immobilised in an inorganic or organic bioresorbable material.

7. The method of claim 5, wherein said pharmaceutically active substance is a dissolved osteoinductive protein.

8. The method of claim 1, 2 or 3, wherein said substance comprises non-active ingredients.

9. The method of claim 1, 2 or 3, wherein said substance comprises calcium phosphates.

10. The method of any of the preceding claims, wherein said drying step comprises isothermal drying.

11. The method of any of the preceding claims, wherein said coating of said device is performed while said device is received within its packaging container.

12. The method of any of the preceding claims, wherein said solution is an aqueous solution or an organic solvent.

13. The method of any of the preceding claims, wherein said solution is an acid aqueous solution.

14. The method of any of the preceding claims, wherein said solution contains an antioxidant.

15. The method of claim 14, wherein said antioxidant is methionin or its derivatives.

16. The method of any of the preceding claims, wherein said device is made of metal or metal alloy, preferably titanium or a titanium alloy.

17. The method of any of the preceding claims, wherein said device is a dental implant, or a coronary stent.

18. The method of any of the preceding claims, wherein step (a) comprises:

(a1) providing a packaging container for said device;

(a2) filling said coating solution into said container;

(a3) inserting said device into said filled container;

wherein the order of steps (a2) and (a3) can be reversed.

19. The method of claim 18, further comprising the steps of:

(A) applying a hydrophobic material onto said inner surfaces of said container, and

(B) heat-curing said applied material to form a baked-in layer on said inner surfaces of said container;

wherein said coating influences the distribution coefficient of the substance to be coated on said device between said container and said device.

20. The method of claim 19, wherein said hydrophobic material is silicone or PTFE.

21. The method of claim 19 or 20, wherein step (A) comprises siliconizing said inner surfaces using silicone emulsion.

22. The method of claim 18, said packaging container comprising a receptacle for receiving said device to be coated, said receptacle being adapted in size and shape to the size and shape of said device.

23. The method of claim 22, wherein the inner surface of said receptacle is coated.

24. The method of any of the preceding claims, further comprising the step of applying a vacuum for removing air bubbles, prior to step (b).

25. The method of any of the preceding claims, wherein step (b) is performed at about 100 hPa at ambient temperature.

26. The method of any of the preceding claims, wherein step (b) is performed using an ice-condenser.

27. The method of any of claims 18 to 26, further comprising the step of evacuating said container, venting it with nitrogen, and closing said container under nitrogen.

28. Packaging container for a device, said packaging container being adapted such that said device is coatable (with a substance) directly within said packaging container, by contacting said device into a solution of said substance, and drying said device while being in contacting said solution.

29. The packaging container according to claim 28, said packaging container being adapted in size and shape to the size and shape of said device.

30. The packaging container according to claim 28 or 29, wherein the inner surface of said packaging container is coated.

31. The packaging container according to claim 30, wherein the inner surface of said packaging container is coated with a layer of an inert, repelling (hydrophobic/or hydrophilic), material.

32. The packaging container according to claim 28, comprising a receptacle for receiving said device to be coated, said receptacle being adapted in size and shape to the size and shape of said device.

33. The packaging container according to claim 32, wherein the inner surface of said receptacle is coated.

34. The packaging container according to claim 33, wherein the inner surface of said receptacle is coated with a layer of an inert, repelling (hydrophobic/or hydrophilic), material.

35. The packaging container according to claim 31 or 34, wherein the hydrophobic material is a silicone.

36. The packaging container according to claim 31 or 34, wherein the hydrophobic material is PTFE.

37. The packaging container according to any of claims 32 to 36, wherein said receptacle is coaxially located within a container housing.

38. The packaging container according to claim 37, wherein said container housing comprises an opening for receiving said device and said coating substance, and a bottom portion being located opposite to said opening, wherein said receptacle comprises an opening for receiving said device and said coating substance, and a bottom portion being located opposite to said opening, said opening of said housing and said opening of said receptacle being aligned with each other, and wherein said receptacle is attached at its bottom portion to the bottom portion of said housing.

39. The packaging container according to claim 38, wherein the opening portion of said receptacle is spaced from the opening portion of said housing.

40. The packaging container according to any of claims 28 to 39, being made of glass.

41. Method of coating the inner surfaces of a packaging container for a device, preferably implants, to be coated by a substance, comprising the steps of:
(A) applying a hydrophobic material onto said inner surfaces of said container, and
(B) heat-curing said applied material to form a baked-in layer on said inner surfaces of said container;
wherein said coating influences the distribution coefficient of the substance to be coated on said device between said container and said device.

42. The method of claim 41, wherein said hydrophobic material is silicone or PTFE.

43. The method of claim 41 or 42, wherein step (A) comprises siliconizing said inner surfaces using silicone emulsion.

44. Coated device, obtainable by a method according to any of claims 1 to 27.

45. The coated device of claim 44, wherein said device is an implant.

46. The coated device of claim 45, wherein said implant is a dental implant.

47. The coated device of claim 45, wherein said implant is a stent, a nail, a cage, a screw, or a plate, respectively.

48. Use of said method of coating a device according to any of claims 1 to 27 for improving the homogeneous distribution of the coating on the device.

49. Use of said method of coating a packaging container according to any of claims 41 to 43 for improving and/or controlling the distribution coefficient of the substance to be coated on said device between said container and said device.

50. A kit comprising the device which is obtainable by the method of any one of claims 1 to 27.